BIIB021, an Hsp90 inhibitor: A promising therapeutic strategy for blood malignancies (Review)

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Abstract. Heat shock proteins (HSPs) are molecular chaperones that are consistently increased to help cells survive under conditions of stress. As a member of the Hsps, Hsp90 is involved in protein post-translational maturation and disposition. This protein is ubiquitously expressed in normal cells. However, in cancer cells and particularly in hematological malignancies, Hsp90 is unexpectedly abundant to maintain levels of proteins vital for cancer pathology. Hsp90 inhibitors can target the ATP domain of Hsp90 and prohibit its exchange of ADP for ATP, leading to the degradation of client proteins and disruption of signaling cascades. Concomitantly, Hsp90 inhibitors induce tumor cell apoptosis, promote cell cycle arrest and abrogate microenvironment-derived cytoprotection. Geldanamycin, a benzoquinone antineoplastic antibiotic isolated from the bacterium *Streptomyces hygroscopicus*, and its derivative, 17-AAG, were first developed as Hsp90 inhibitors and exhibited effective anticancer potency. Whereas, severe side effects and low solubility restricted their application at the clinical level, BIIB021, a novel and fully synthetic inhibitor of Hsp90, is water soluble and well-tolerated. Beyond degrading oncogenic protein, BIIB021 can overcome multidrug resistance and potentiate the effects of other therapeutics. phase I/II trials have been conducted to evaluate the dosing schedules and activity of this agent. The present review focuses on the antitumor profile of BIIB021. Furthermore, given the promising efficacy of BIIB021 in leukemia and lymphoma, this review also discusses current research concerning the treatment of hematologic malignancies by targeting Hsp90.

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Abbreviations: HSPs, heat shock proteins; CML, chronic myeloid leukemia; CLL, chronic lymphocytic leukemia; GA, geldanamycin; 17-AAG, 17-allylamino-17-desmethoxy-geldanamycin; RD, radicicol; TKIs, tyrosine kinase inhibitors; HL, Hodgkin's lymphoma; KSHV, Kaposi sarcoma-associated herpes virus; PEL, primary effusion lymphoma; LMP1, latent membrane protein 1; EBV, Epstein-Barr virus; T-ALL, T-cell acute lymphoblastic leukemia; TPL, triptolide; MDS, myelodysplastic syndrome; GISTs, gastrointestinal stromal tumors; PR, partial response; MTD, maximum tolerated dose; DLT, dose-limiting toxicity; LANA, latency-associated nuclear antigen; KS, Kaposi sarcoma; HNSCC, head and neck squamous cell carcinoma; WDTC, well-differentiated thyroid carcinoma; AML, acute myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; TYK2, tyrosine kinase 2; MCL, mantle cell lymphoma; MPNs, myeloproliferative neoplasms; ATL, adult T-cell leukemia-lymphoma; MM, multiple myeloma; BMSCs, bone marrow stromal cells; CSCs, cancer stem cells; Ara-C, cytarabine; CR, complete response; CRi, incomplete blood count recovery; DIC, disseminated intravascular coagulation; ARDS, acute respiratory distress syndrome; SD, stable disease; PTCL, peripheral T-cell lymphoma

Key words: cancer, heat shock protein 90, BIIB021, blood malignancies, clinical trial

Contents

1. Introduction

Heat shock proteins (HSPs) can be found in all cells and are key elements in the process of protein synthesis. When cells are exposed to stressors, protein misfolding, aggregation or denaturation may occur resulting in cell death. Under such difficult conditions, the expression of HSPs are increased and facilitate cell survival (1,2).

Hsp90 is a member of the HSPs and is important in protein post-translational maturation and disposition. Its N-terminal domain contains a characteristic Bergerat fold (unique structural ATP-binding domain). Binding and hydrolysis of ATP induces conformational changes to Hsp90, and this allows for the binding of Hsp90 to its client proteins to help them fold their active conformation. Hsp90 inhibitor targets the ATP domain and disrupts the exchange of ADP for ATP of Hsp90 protein, thereby causing client proteins to undergo misfolding, ubiquitination and subsequent degradation by the proteasome pathway.

Hsp90 is evolutionarily conserved and ubiquitously expressed in normal cells, accounting for as much as 1-2% of total cellular protein (3). Cancer cells, particularly hematological malignant cells, express 2- to 10-fold higher levels of Hsp90 than normal cells. Many of its client proteins are signal transducers that are essential for tumor cell proliferation, survival and generation (3). In fact, Hsp90 is important in the acquisition and maintenance of the malignant phenotype for its unique function in transformation maintanence and growth facilitation. Moreover, cancer cells are exposed to numerous harsh conditions and rely on the function of Hsp90 to survive. As a consequence, it is rational to apply Hsp90 inhibitors in the treatment of malignancies (4,5). Hsp90 inhibitors can target estrogen and progesterone receptors in breast cancer (6,7), ERBB2 in ERBB2-driven xenograft models (8,9), androgen receptor in hormone-sensitive metastatic prostate cancer (10,11), BRAF in melanoma and colon cancer (12-15), EGFR in non-small cell lung cancer (16), Bcr-Abl in chronic myeloid leukemia (CML) (17), ZAP-70 in chronic lymphocytic leukemia (CLL) (18) and c-KIT in gastrointestinal stromal tumors (19).

Over the past few years, numerous efforts have been made to discover Hsp90 inhibitors from derivatives of natural products to fully synthetic small molecules. Geldanamycin (GA), first isolated from *Streptomyces hygroscopicus* as an antibiotic in 1970, can bind specifically to the ATP pocket of Hsp90 by positioning the benzoquinone ring to the entrance of the binding pocket and the ansa ring towards the bottom of the pocket (20). Once appropriately positioned, GA forms hydrogen bonds with the pocket and restrains Hsp90 in its ADP-bound conformation. This leads to immaturation and degradation of the client proteins by the proteasomal pathway (21,22). GA has exhibited effective anticancer potency in pre-clinical studies. Yet, it has never been evaluated at the clinical level as it displays severe hepatotoxicity (stemming from the benzoquinone moiety), metabolical and chemical unstability and very low solubility in aqueous solution (23).

17-Allylamino-17-desmethoxy-geldanamycin (17-AAG) inhibited Her2 in breast cancer cells with IC_{50}=31 nM and is the first GA derivative that has proceeded to clinical trials (24). Disappointingly, the toxic profile of 17-AAG restricts its application (25). Moreover, this agent has limited solubility in water and shows reduced activity in some multidrug-resistant cells.

Radicicol (RD) is a macrocyclic lactone antibiotic originally isolated from the fungus *Monosporium bonorden* in 1953 (26). The co-crystal structure of RD with yeast Hsp90 shows that RD can exhibit a C-shaped conformation similar to ADP and then competitively bind to the N-terminal ATP pocket of Hsp90 (21). Thus, it restrains Hsp90 in its ADP-bound conformation and leads to degradation of client proteins, similar to GA. It has antitumor effects *in vitro*, but no *in vivo* efficacy has been noted due to its instability in serum (27). A series of RD analogs have been synthesized and evaluated at preclinical and clinical levels.

PU3 [9-butyl-8(3,4,5-trimethoxy-benzyl)-9H-purin-6-ylamine], the first reported synthetic purine-scaffold inhibitor, was designed by Chiosis and colleagues (28) (Fig. 1). In a manner similar to GA, PU3 can induce protein degradation. Yet, PU3 is not as potent as 17-AAG.

Based on the structure of PU3, the aryl substituent was shifted from 8- to the 9-position along with the NH2 from the 6- to the 2-position. Since the 9-benzyl series had poor aqueous solubility, the phenyl ring was replaced with a 2'-pyridyl group (29). BIIB021, the 3',5'-dimethyl-4'-methoxy-2'-pyridyl derivative, is soluble in biological fluids (Fig. 1). The binding affinity of BIIB021 was found to be 1.7±0.4, better than that of 17-AAG (4.6±0.5 nmol/l) (30). The drug is selective for Hsp90 over kinases and another ATPase. Even at a low nanomolar concentration, BIIB021 can inhibit the growth of cancer cells, such as N87, MCF-7 and BT474, with IC_{50} values ranging from 60 to 310 nmol/l. It also exhibited antitumor effects in a xenograft model. As long as 48 h after treatment, the compound can be detected in tumor tissues despite its short half-life in serum. The effects of BIIB021 can last for more than 24 h. This provides the possibility of flexible dose regimen to lessen dose-limiting hepatotoxicity. Furthermore, the cytotoxic activity of BIIB021 is not influenced by efflux pump, loss of NQO1 or Bcl-2 overexpression, avoiding the limitations of 17-AAG (31).

In conclusion, BIIB021 is a promising Hsp90 inhibitor. This review focuses on the utility of BIIB021 in a wide variety of cancers, especially in hematologic malignancies, and its underlying mechanisms. In addition, this review is followed by a discussion of current research on the application of Hsp90 inhibitors in blood malignancies.

2. Effects of BIIB021 in hematologic malignancies

Chronic myeloid leukemia. The majority of chronic myeloid leukemia (CML) cases are characterized by a fusion oncoprotein (Bcr-Abl) derived from the reciprocal translocation between chromosomes 9 and 22. Protein-tyrosine kinase expressed by this fusion protein activates several intracellular signaling pathways that prevent cells from apoptosis and promote cell proliferation. The introduction of tyrosine kinase inhibitors (TKIs) has dramatically improved the prognosis of CML patients. Yet, following the wide use of TKIs, almost 30% of patients have developed resistance to the standard treatment of imatinib. This phenomenon is attributed to mutations in the kinase domain, genomic instability and Bcr-Abl amplification, especially the T315I mutation even insensitive to the first and second generation of TKIs (32). The third generation TKIs, ponatinib, has antileukemia effect against CML cells with mutated Bcr-Abl including T315I. However, the risk of serious thromboembolic events restricts its application (33). Novel approaches therefore should be developed to override TKI resistance. Indeed, Bcr-Abl has been confirmed as a client protein of Hsp90 (34). Inhibitors of Hsp90 can destabilize the binding of Bcr-Abl protein thus resulting in formation of heteroprotein that is degraded via the ubiquitin proteasomal pathway (34).

A series of CML cell lines including T315I mutant were quite sensitive to BIIB021 (35). This drug inhibited cell proliferation and induced caspase-dependent apoptosis. Moreover, the oncoprotein Bcr-Abl was degraded and several signaling pathways were downregulated, including JAK/STAT and Akt. BIIB021 decreased the nuclear and cytoplasmic levels of β-catenin, a factor essential for survival and self-renewal of leukemic stem cells and blockage for the achievement of molecular remission in CML patients (36). Notably, BIIB021 triggered autophagy in CML cells independent of Beclin-1.

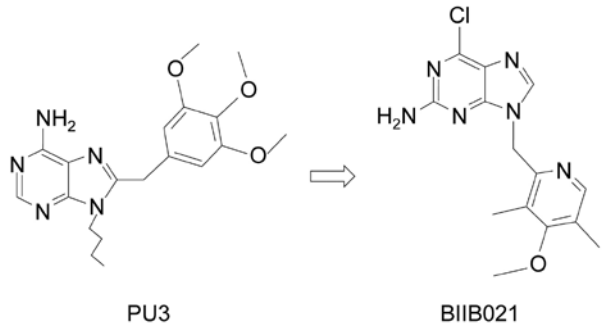

Figure 1. Chemical structures of PU-3 [9-butyl-8(3,4,5-trimethoxy-benzyl) -9H-purin-6-ylamine] and BIIB021 [6-chloro-9-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-9*H*-purin-2-amine].

Following exposure to BIIB021, the expression of Beclin-1 was decreased. This was contributed to activated caspase which cleaved Beclin-1 and the N-terminal fragment of Beclin-1 in turn suppressing autophagy (37,38). In fact, BIIB021 targeted mTOR complex 1 to influence Ulk1 phosphorylation and eventually initiated autophagy. Pretreatment of autophagy inhibitor (3-methyladenine or bafilomycin A1) effectively increased the rate of BIIB021-mediated cell death and apoptosis. This suggested a possibility: BIIB021 combined with autophagy inhibitors in a regimen would achieve optimized therapeutic effect against imatinib-sensitive and -resistant CML, including cells harboring T315I-mutant Bcr-Abl.

Lymphomas. Lymphoma is one of the most frequently diagnosed human cancer. It may be divided into non-Hodgkin (90%) and Hodgkin (10%) subtypes. A total of 90% of lymphomas are of B-cell origin while some can be derived from T-cell or natural killer cells. Even though treatment of Hodgkin's lymphoma (HL) has already achieved great success, ~2% of patients with HL are refractory to traditional therapy and 13% of patients suffer relapse (39). Hence, novel therapies are urgently needed. Current research indicates that Hsp90 is highly expressed in HL cells and promotes tumor survival by supporting the activation of NF-κB signaling (40-42). One previous study illustrated that BIIB021 induces a decrease in NF-κB activity by 14-70% in HL cells with mutated IκB or functional IκB. This means that BIIB021 inhibits the constitutionally active NF-κB in HL cells despite IκB mutations. Moreover, Böll *et al* (43) observed that BIIB021 decreased HL cell viability and had additive effects with traditional chemotherapy (doxorubicin and gemcitabine). Furthermore, this type of Hsp90 inhibitor increased the susceptibility of HL cells against NK cell attack. Indeed, in response to BIIB021, researchers observed enhanced expression of NKG2D-specific ligands (MICA/B and ULBP2) on tumor cells. This in turn increased NK cell-related cytotoxicity of HL cells and may have a profound impact on the immune system and antitumor effects (44,45). In accordance with the *in vitro* effects, BIIB021 also inhibited tumor growth *in vivo*.

In addition to HL, BIIB021 has shown efficacy against Kaposi sarcoma-associated herpes virus (KSHV)-associated primary effusion lymphoma (PEL) cells. PEL is a type of aggressive non-HL with poor prognosis. It is characterized by KSHV infection and frequently occurs in immunocompromised patients (46). Although a cytotoxic chemotherapeutic regimen is available to cure PEL, the prognosis of this disease is extremely poor and new therapeutic strategies must be found. Treatment with BIIB021 induced cell cycle arrest and apoptosis in PEL cells, by decreasing the level of several proteins critical for cell cycle regulation (CDK, c-MYC and cyclin) and pathogenesis of the disease (AKT, GSK3β and survivin) (47). As NF-κB activity is essential for the survival and proliferation of PEL cells, researchers demonstrated that BIIB021 can block the constitutive NF-κB pathway. On the one hand, BIIB021 reduced the level and activity of IKKα/IKKβ to influence the classical NF-κB pathway. On the other hand, the Hsp90 inhibitor disrupted the K13-IKK complex resulting in down-regulation of vFLIP and K13 and blockage of K13-related NF-κB activation. Moreover, the inability of BIIB021 to induce expression of lytic genes and inhibition of their expression alleviated the safety concern of lytic reactivation for KSHV lytic gene replication and transcription which are crucial to KSHV tumorigenesis. The antiproliferative effects were also evaluated in a mouse xenograft model. Compared with control vehicle, BIIB021 significantly reduced tumor volume and prevented development of splenomegaly.

More recently, it has emerged that BIIB021 is a candidate suppressor of latent membrane protein 1 (LMP1) expression which is a major oncogene encoded by the Epstein-Barr virus (EBV) (48). EBV can infect B cells, T cells and NK cells and is closely connected with immune cell malignancies. BIIB021 decreased the viability, induced apoptosis and caused cell cycle arrest of T and NK cell lines, including EBV-positive T cell lines (SNT13 and SNT16) and NK cell lines (KAI3 and SNK6). The drug also had a similar effect on Jurkat and KHYG1 which are EBV-negative counterparts. The protein level of LMP1 downstream targets was decreased, such as NF-κB, JNK and Akt. A murine xenograft model was used to demonstrate that BIIB021 can inhibit the growth of EBV-positive NK cell lymphomas *in vivo*.

T-cell acute lymphoblastic leukemia. T-cell acute lymphoblastic leukemia (T-ALL) is a clinically aggressive hematologic malignancy that accounts for 25% of adult ALL and 15% of pediatric cases (49). Limited targeting therapies are available for this type of disease at present. Li *et al* (50) reported that BIIB021 can inhibit the growth and induce the apoptosis of Molt-4 cells (a human T-ALL cell line) at low nanomolar concentrations. Notably, the drug disrupted the interaction between p53-MDM2 by suppressing the expression of MDM2 while increasing the level of p53. This resulted in p53-mediated apoptosis. Co-treatment with BIIB021 and triptolide (TPL) exhibited a synergetic inhibitory effect on the proliferation of Molt-4 cells. This phenomenon may be because TPL can activate p53 without influence on MDM2 levels. Therefore, the co-treatment markedly enhanced p53 activation and upregulated the expression of several Bcl-2 family members (Bak and Bim).

Myelodysplastic syndrome. Researchers have previously reported that, compared with healthy subjects and low-risk myelodysplastic syndrome (MDS) patients, the level of Hsp90 is overexpressed in high-risk counterparts and is associated with a poor outcome. A preclinical trial examined the antitumor

activity of BIIB021 on an MDS cell line (SKM-1) (51). Following BIIB021 treatment, SKM-1 cells were arrested in the G1 phase of the cell cycle and underwent apoptosis. Furthermore, the study also indicated that the mechanisms of apoptosis were attributed to a decrease in phosphatidylinositide 3-kinase/Akt and nuclear factor-κB pathway. All of the above findings imply that BIIB021 may be a new available strategy for high-risk MDS.

3. Effects of BIIB021 in solid tumors

Gastrointestinal stromal tumors. Gastrointestinal stromal tumors (GISTs) are one of the most common mesenchymal cancers of the digestive system (52). Activating mutations in KIT and PDGFRα, two receptor tyrosine kinases, are the key element in the development and progression of GISTs. Specific mutations are associated with the therapeutic response to imatinib and sunitinib; however, most tumors ultimately become resistant to these drugs due to secondary kinase mutations or alternative activated pathways (53,54). KIT and PDGFRα are client proteins of Hsp90 for their mutated forms rely on Hsp90 to stabilize (55). Inhibition of Hsp90 can result in the degradation of any form of these kinases. A phase II study evaluated the antitumor activity of BIIB021 in GIST patients (56). Twenty-three patients were stratified into two groups: 12 subjects received 600 mg twice weekly (b.i.w.) while 11 subjects were administered 400 mg three times weekly (t.i.w.). All patients had received prior treatment and had acquired resistance to imatinib and sunitinib. By evaluating the change from baseline (before day 1) to the end of one cycle (day 29), 5 patients had a decline of >25% in SUVmax and achieved a partial response (PR). Among them, 3 of 12 patients (25%) were from 600 mg b.i.w. cohort and 2 of 11 patients (18%) received 400 mg t.i.w. Another 9 patients suffered a lower decrease in SUVmax although they did not meet the PR criterion. Moreover, the study also suggested that a more frequent dose of BIIB021 may induce better antitumor effect. The agent was generally well tolerated as most of the drug-related adverse events were less than grade 2. Compared with ansamycin derivatives such as IPI-504, treatment of BIIB021 did not induce severe hepatotoxicity.

Advanced solid tumors. Patients were treated with BIIB021 in a phase I dose-escalation trial with advanced solid tumors refractory to standard treatment (57). A total of 60 patients were enrolled in the study. The study determined the maximum tolerated dose (MTD) and safety of this Hsp90 inhibitor on two schedules: Twice a week for 3 weeks followed by 1 week off and twice a week for 4 weeks in continuous 28 day cycles. In schedule 1, 50 subjects were given a dose ranging from 25 to 800 mg and BIIB021 was found to be well tolerated at doses up to 700 mg twice a week. Dosed with 800 mg, two cases of dose-limiting toxicity (DLT) were observed: Syncope and dizziness. Based on the clinical information collected in schedule 1, 6 subjects received a dose of 600 and 700 mg in schedule 2. An MTD was not established in this schedule formally, whereas the 6 patients tolerated these doses. The most common adverse events, defined as occurring in >20% of patients, were nausea, hot flashes, vomiting and dizziness. These events were mild or moderate.

Kaposi sarcoma. Latency-associated nuclear antigen (LANA) is essential for Kaposi's sarcoma-associated herpesvirus (KSHV) genome persistence and Kaposi sarcoma (KS) tumorigenesis (58,59). Recently, Chen *et al* (60) determined that KSHV LANA is a client protein of Hsp90 and ATP-competitive Hsp90 inhibitors disrupted the association between Hsp90 and LANA for Hsp90 bound the N-terminal domain of LANA. This led to degradation of LANA through the ubiquitin-based proteasome pathway. Depletion of Hsp90 by shRNA induced the apoptosis of PEL cells. *In vitro* studies demonstrated that BIIB021 suppressed the proliferation of KS cells (SLK-KSHV, L1T2, SLK and KS-IMM) and decreased the expression of ephrin-B2 and EphA2 at low nanomolar concentrations. Remarkably, compared with KSHV-negative SLK cells, KSHV-positive counterparts were more sensitive to the Hsp90 inhibitor. Colony formation assays and cell cycle analysis further verified the antitumor potency of BIIB021. In addition, KSHV-infected L1T2 cells were injected into SCID mice to establish a xenograft KSHV tumor model. Compared to the negative control, the growth of tumors was notably retarded following treatment of Hsp90 inhibitor (AUY922) at a dose of 50 mg/kg. Immunohistochemistry showed declined levels of LANA and ephrin-B2.

Squamous cell carcinoma. Every year, there are ~600,000 newly diagnosed cases of head and neck squamous cell carcinoma (HNSCC) reported. At present, the standard treatment includes surgery and/or radiotherapy. Radiotherapy is mainly applied to patients with advanced disease and chemotherapy is concomitantly used to increase the efficacy. Recently, BIIB021 has been found as a new adjuvant agent that enhances the sensitivity of HNSCC cell lines to radiation (61).

BIIB021 showed better anti-proliferative effects in 4 cell lines with a mean IC_{50} value of 250 nM, superior to 17-AAG. Compared with each treatment alone, co-treatment with BIIB021 effectively increased the radiation-related cell death and apoptosis even in radiation-resistant cell lines, by downregulating several oncogenic proteins including EGFR, c-Raf-1 and Akt. Moreover, BIIB021 enhanced the G2/M cell population in response to radiotherapy independent of the p53 status.

In xenograft models, the tumors grew much smaller in the combination arm. Tumor sizes remained stabilized following 3 weeks of treatment with BIIB021 or radiation alone while the volume of tumors showed regression after 4 weeks with the combination treatment.

Furthermore, BIIB021 potentiated a significant therapeutic window of radiation to esophageal squamous cell carcinoma cell lines by influencing apoptosis and the cell cycle (62). BIIB021 dramatically decreased the levels of radio-resistance-related proteins such as EGFR, Akt and Raf-1.

Thyroid carcinoma. Although well-differentiated thyroid carcinoma (WDTC) is a type of tumor associated with a good prognosis, 2/3 of cases of metastatic WDTC are refractory. Meanwhile, patients with anaplastic thyroid carcinoma exhibit poor outcome as the tumors are highly aggressive. Recently, research illustrated that BIIB021 induced the cell death of thyroid carcinoma cell lines (8505C and TPC-1) by degrading Hsp90 client proteins. Furthermore, cotreatment

with BIIB021 and histone acetyltransferase inhibitor triptolide demonstrated a combined effect in regards to cytotoxicity induction. This synergism was contributed to inhibition of the PI3K/Akt/mTOR and NF-κB signaling pathways, a decrease of survivin, xIAP and cIAP and promotion of DNA damage (63).

4. Targeting Hsp90 in hematologic malignancies

The promising antitumor potency of BIIB021 in leukemia and lymphoma motivates the focus of this inhibitor for the treatment of blood malignancies by targeting Hsp90.

A high level of Hsp90 has been observed in leukemia and myeloma (64-67). The Hsp90 level in plasma can be used as a biomarker of leukemia engraftment and progression (68). Overexpression of the protein is correlated with poor prognosis and chemotherapy resistance in acute myeloid leukemia (AML) (69). Furthermore, Hsp90 is required to maintain the stability and function of oncogenic proteins such as c-KIT and FLT3-ITD in AML and Bcr-Abl in CML (70). Inhibition of Hsp90 extensively influences a variety of signaling proteins involved in cell apoptosis, survival and differentiation. Hence, it is reasonable to use Hsp90 inhibitors for the treatment of hematologic malignancies.

Preclinical studies

Control of apoptosis and cell cycle. Treatment with Hsp90 inhibitors could induce apoptosis by activating the mitochondrial caspase pathway and regulating Bcl-2 family proteins (50,71).

In diffuse large B-cell lymphoma (DLBCL), endogenous Hsp90 interacts with Bcl6 and stabilizes Bcl6 at both the transcription and protein level. Apoptosis was observed after treatment with the Hsp90 inhibitor, PU-H71. The drug preferentially accumulated in lymphomas and suppressed Bcl6-dependent DLBCL xenografts (72). Recently, a novel oncogenic pathway was found which promotes the aberrant survival of T-ALL cells, i.e. tyrosine kinase 2 (TYK2)/phospho-STAT1/Bcl2 pathway (73). TYK2, as a member of the JAK tyrosine family, is a client protein of Hsp90 (74,75). An Hsp90 inhibitor NVP-AUY922 effectively degraded TYK2 and resultantly decreased phospho-STAT1 and Bcl2, a pro-survival protein. Meanwhile, the drug increased pro-apoptotic proteins Bim and Bad (76).

Furthermore, Hsp90 inhibitors are able to regulate the cell cycle. Mantle cell lymphoma (MCL) is characterized by the overexpression of cyclin D1 and abnormal regulation of the cell cycle. Treatment with Hsp90 inhibitors induced G0/1 arrest in MCL cells and decreased cell cycle regulatory proteins, including cyclin D1, cdk4, p21 and CHK1 (77,78).

Degradation of oncoprotein and disruption of signaling transduction. FLT3-ITD and point mutation occur in 25-30% of AML patients and are associated with poor prognosis. Meanwhile, FLT3-ITD is a client protein of Hsp90. 17-AAG induced polyubiquitination and proteasomal degradation of FLT3-ITD and mutants by disrupting its association with Hsp90 (79,80). Downstream signaling of FLT3-ITD such as JAK-STAT and PI3K/AKT was also decreased (81). In addition, 5% of AML patients have KIT mutations and activated KIT kinase plays an essential role in the pathophysiology of the disease (82). 17-AAG and GA were found to suppress the growth of cells expressing D816V-KIT (83).

The oncoprotein Bcr-Abl is involved in the pathogenesis of Bcr-Abl$^+$ human leukemia including CML and Ph$^+$ ALL. Bcr-Abl is a client protein of Hsp90, and Hsp90 inhibitors have been developed as novel approaches for the treatment of Bcr-Abl$^+$ leukemia especially in relapsed or IM-resistant cases. Hsp90 inhibitors were found to induce Bcr-Abl degradation and this was accompanied by inhibition of downstream signaling (JAK/STAT, Akt and β-catenin) including cells expressing T315I mutation (35,84,85). A novel Hsp90 inhibitor IPI-504 was found to effectively inhibit the survival and proliferation of leukemic stem cells which is a potential reason for relapse (86). The drug prolonged the survival period of mice bearing Bcr-Abl T315I-induced leukemia. In addition, Hsp90 inhibitors exerted a combined effect with TKIs (87,88).

Bcr-Abl-negative myeloproliferative neoplasms (MPNs) are a group of stem cell diseases that include polycythemia vera, essential thrombocytosis and primary myelofibrosis. In the majority of patients with MPNs, a mutation in the JAK2 kinase (*JAK2V617V*) is always detected with constitutive activation of the JAK2-STAT pathway which is independent of growth factors. This allows hematopoietic cell proliferation in the absence of cytokines. However, JAK2 inhibitors show limited efficacy in the clinic. Hsp90 inhibitors have been evaluated for the treatment of MPNs in preclinical studies, considering JAK2 is a client protein of Hsp90. PU-H71, a new Hsp90 inhibitor, induced degradation of JAK2, inhibited JAK-STAT signaling and triggered cell apoptosis in JAK2 mutant cell lines and primary patient samples. PU-H71 also had the potency to improve the survival period in mouse bone marrow transplant models by disrupting JAK2 stability, without toxic effects on normal hematopoiesis (89).

As the most common leukemia in the Western world, B-cell CLL is a malignancy of mature B cells expressing T-cell antigen CD5. The disease is characterized by elevated expression of several Hsp90 client proteins making Hsp90 a potential therapeutic target. At the molecular level, Hsp90 inhibitors led to depletion of Akt, IKK and NF-κB, accompanied by a decline in NF-κB target gene (MCL1, CFLAR, BIRC5 and BCL2) transcription and apoptosis in a caspase-dependent manner (90,91). Compared with normal B lymphocytes, Lyn is overexpressed, abnormally exists in the cytosol of B-CLL and shows high activity which mediates signaling cascade triggered by BCR. As Hsp90 binds to the catalytic domain of Lyn, treatment with GA triggers the cytosolic Lyn complex destabilizes in the early phases of apoptosis and resultantly inactivates cytosolic Lyn (92). Recently, research indicated that SOCS3 acts as a regulator of important cell survival pathways in CLL. By activation of p38 signaling, 17-DMAG increased the SOCS3 level and in turn prohibited phosphorylation of AKT and STAT3, thus inducing blockage of cell migration and survival in CLL (93).

Adult T-cell leukemia-lymphoma (ATL) is a chemoresistant malignancy with an origin from CD4$^+$CD25$^+$ T lymphocytes linked to HLTV-1. Tax, encoded by the HTLV-1 genome, can control HTLV-1 replication and advance oncogenic transformation of T lymphocytes. Recently, research indicated that Hsp90 is a binding partner of Tax. Downregulation of Hsp90 by 17-DMAG or shRNAs provoked

Tax degradation and this was accompanied by attenuation of NF-κB and HTLV-1 LTR activation. Thus, 17-DMAG suppressed HTLV-1 replication and led to apoptosis in cell lines and primary ATL cell samples (94,95). The drug has no apparent effects on normal PBMCs. In addition, PIM kinases and the β-catenin/TCF7L2 pathway underwent a decrease and resultantly these contributed to Hsp90 inhibitor-associated cell apoptosis in ALT cells (95,96). In an ATL mouse model, 17-DMAG administration reduced infiltration of tumor cells into organs, inhibited *de novo* viral production and prolonged the survival period (97).

Abrogation of micro-environment protection. Hematological malignancies always develop in the bone marrow and secondary lymphoid organs. These microenvironments are characterized by various stromal and T cells that are essential to cancer cell survival and drug resistance. Microenvironment-targeted treatment has emerged and gained attention in hemato-oncology.

In multiple myeloma (MM), 17-AAG suppressed the expression of IGF1R and IL-6R on the cell surface and their downstream signaling including IKK/NF-κB, PI-3K/Akt and Raf/MAPK. Such effects abrogated the protection of bone marrow stromal cells (BMSCs) on MM tumor cells and made them sensitive to other anticancer agents (66). Furthermore, treatment with SNX-2112 was able to overcome the protective effects derived from cytokines and BMSCs. This is because SNX-2112 inhibited Akt and MEK/ERK pathway even in the presence of exogenous IL-6, IGF-1, or BMSCs and block the formation of capillary-like tubes by suppression of eNOS/Akt. In addition, as osteolytic bone destruction is a common complication of MM, SNX-2112 has the potency to markedly inhibit osteoclastogenesis by downregulation of ERK/c-fos and PU.1 (98). Exposure of Hsp90 inhibitor (KW-2478) to MM cells induced a decrease in IgH translocation products (FGFR3, c-Maf and cyclin D1). In a MM orthotopic model, KW-2478 not only decreased the M protein level in serum but also reduced tumor burden in bone marrow (99).

Within bone marrow and lymph nodes, CLL cells are mixed with numerous T lymphocytes expressing CD40 ligand and IL-4. Together with BMSCs and follicular dendritic cells, these cells can protect CLL cells from chemotherapy-related apoptosis *in vitro*. Co-cultured CLL cells with NTL or CD40L cells abrogated fludarabine's ability to kill cells and dasatinib resistance also occurred in NTL or CD154L/IL-4 co-culture system. By comparison, Hsp90 inhibitor NVP-AUY922-AG retained its toxicity under the same condition by decreasing IKKα, IKKβ, regulators of NF-κB, and retarding the transcription of NF-κB target genes MCL1, CFLAR and BIRC5. Considering fludarabine activation of MCL1 and BIRC5, Walsby *et al* (91) treated NVP-AUY922 with fludarabine and found that this Hsp90 inhibitor potentiated CLL cell sensitivity to fludarabine. This combination maintained the net transcriptional repression of MCL1, CFLAR and BIRC5, providing a potential explanation for the synergy. The same synergistic effect was also observed following cotreatment of 17-DMAG with dasatinib (100).

Overcoming drug resistance. Initially, there is only a minority of CLL patients at diagnosis who present with TP53 mutation or deletion. However, such defects are frequently obtained during the disease course and induced p53 defects are strongly associated with resistance to alkylating agents and purine analogues, the mainstay of current treatment. Treatment with GA depressed the overexpressed mutant p53 protein while increased the level of wt counterparts. These phenomena were ATM-independent and linked to a decrease in Akt and activation of MDM2. p21, a potent inducer of cell cycle arrest, was upregulation without dependence of p53/ATM. Cytotoxicity studies demonstrated that Hsp90 inhibitors prohibited the proliferation of cell lines and patient samples (101,102). It was suggested that Hsp90 inhibitor abrogated chemo-resistance in CLL with TP53 defects for it killed cells independent of ATM or TP53 mutations. Furthermore, SNX-7081, a synthetic Hsp90 inhibitor, synergized with fludarabine against CLL cells as evidenced by a significant reduction in the IC_{50} value of fludarabine to within a clinically achievable range and a decrease in cell viability (103).

As described above, inhibitors of JAK2 have been developed for the treatment of MPNs, *CRLF2*-rearranged B-ALL and other tumors with activated JAK2 signaling. Research has indicated that cells expressing G935R, Y931C and E864K mutations near the ATP-binding region of the JAK2 kinase are resistance to a panel of JAK inhibitors, whereas, these mutations had little influence on tumor cell sensitivity to Hsp90 inhibitors. In fact, AUY922 degraded both wild-type and mutant type of JAK2. AUY922 also exhibited 100- to 1,000-fold more potency against B-ALL cells harboring *CRLF2* rearrangements than an enzymatic JAK2 inhibitor for the Hsp90 inhibitor has multi-targets (104).

Eradication of stem cells. Cancer stem cells (CSCs) are a subpopulation of cancer cells with properties of quiescence, self-renewal and persistent proliferation. CSCs are the key contributors to drug resistance as well as relapse and metastasis (105).

At low concentrations, 17-AAG has the ability to eliminate lymphoma stem cells *in vitro* and *in vivo*, as the drug disrupts Hsp90-mediated mRNA expression and transcriptional activity of HSF1α (106). Peng *et al* (86) isolated bone marrow cells from mice with CML expressing T315I and showed that treatment with IPI-504 had a marked inhibitory effect on stem cells while IM had little influence. Efficacious anti-CSC potency of IPI-504 was also observed in mouse models without inhibition of normal CSCs. Hsp90 inhibitor decreased β-catenin, a factor essential for survival and self-renewal of leukemic stem cells (36). In addition, co-treatment with Hsp90 inhibitor and SIRT1 inhibitor exhibited a combined effect on chemo-resistant stem-like cells of CML (107). Depletion of SIRT1 prohibited the 17-AAG-mediated induction of Hsp70/Hsp27 and BCRP-mediated activity of 17-AAG efflux and reduced the levels of CD44, Oct-4, β-catenin, c-Myc and mut-p53.

Combined effects. Hsp90 inhibitors exert a synergistic effect together with traditional or targeted chemotherapeutic agents including doxorubicin, bortezomib, PI3K inhibitor, Akt inhibitor, IBP inhibitor, rapamycin and HDACi (108-113). Recently, it was found that PU-H71 can target BCR signaling, and subsequently attenuate kinase phosphorylation, calcium signaling and NF-κB activity. Combined exposure to PU-H71

Table I. Reported clinical studies of Hsp90 inhibitors in blood malignancies.

Blood malignancies	Hsp90 inhibitor	Phase	Patient no.	DLTs	Findings
Acute leukemia	17-DMAG	I	24	Cardiac ischemia	MTD was 24 mg/m^2 twice weekly; 3/17 achieved CR with incomplete blood count recovery
B cell malignancies	KW-2478	I	27 (22 MM and 5 nNL)	No DLTs	MTD was not reached; 24/25 (96%) achieved SD with 5 being free of disease progression for ≥6 months
Relapsed lymphoma	17-AAG	II	22 (13 cHL and 9 MCL)	-	7/18 (39 %) demonstrated tumor reduction, 2/18 achieved PR
CLL	17-DMAG	I	15	No DLTs	MTD was not reached, 3/15 achieved SD
nHL	AUY922	II	20 (14 DLBCL and 6 PTCL)	-	1/14 achieved CR in DLBCL and 1/6 achieved PR in PTCL; 13/20 received only 1 cycle of AUY922 or less due to apparent disease progression
MM	NVP-AUY922	I	24	Blurred vision	No MTD was reached, 16/24 had SD
MM	17-AAG+ bortezomib	I/II	72	Hepatotoxicity, renal failure, metabolic acidosis	MTD was 17-AAG 340 mg/m^2 and bortezomib 1.3 mg/m^2; 2/67 achieved CR, 8/67 achieved PR, 8/67 had a minimal response and 22/67 had SD
MM	NVP-AUY922+ bortezomib	IB	5	Musculoskeletal pain, diarrhea, atypical noncardiac chest and musculoskeletal pain	1/5 had PR, 4/5 had SD
Acute leukemia	17-AAG+ Ara-C	I	26	DIC, ARDS, myocardial infarction	MTD was Ara-C 400 mg/m^2/day for 5 days along with 17-AAG 300 mg/m^2 on days 3 and 6; 2/21 had CR, 4/21 had PR

DLT, dose-limiting toxicity; MTD, maximum tolerated dose; MM, multiple myeloma; nNL, non-Hodgkin lymphoma; cHL, classical Hodgkin lymphoma; MCL, mantle cell lymphoma; PR, partial response; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; PTCL, peripheral T-cell lymphoma; CR, complete response; Ara-C, cytarabine; SD, stable disease; DIC, disseminated intravascular coagulation; ARDS, adult respiratory distress syndrome.

and ibrutinib, a BCR pathway inhibitor, induced synergistic killing of DLBCL cell lines (114).

Bortezomib has been introduced to the treatment of relapsed/refractory MCL for it can induce cell death through upregulation of the BH3-only proapoptotic protein Noxa and generation of reactive oxygen species rather than dependence on the NF-κB pathway, whereas, not all patients respond to the drug and resistance often appears. Based on an analysis of 18 MCL samples, Roue *et al* (115) found that these phenomena may result from an increase in pro-survival chaperone Bip/Grp78 of which stabilization is dependent on Hsp90. Simultaneous exposure to IPI-504 and bortezomib abrogated the association between Hsp90 and Bip, then activated the ER stress pathway and ultimately restored MCL cell sensitivity to bortezomib both *in vitro* and *in vivo*. This combination deserves further research at the clinical level.

In primary AML blasts, the 50% lethal dose of Hsp90 inhibitor (NVP-AUY922-AG) was observed at concentrations 2 logs lower than cytarabine (Ara-C) which is a traditional chemotherapy agent. There was a synergistic decrease in the proliferation of AML cells and 20/25 primary samples following co-treatment with the two agents (116,117). This was due to the fact that Ara-C, even at low concentrations, induced activation of Chk1 which facilitated cell survival. Conversely, following treatment of 17-AAG for 24 h, the expression of Chk1 was depleted. This was accompanied by diminished Ara-C-related S phase accumulation and decreased Cdc25A degradation (118).

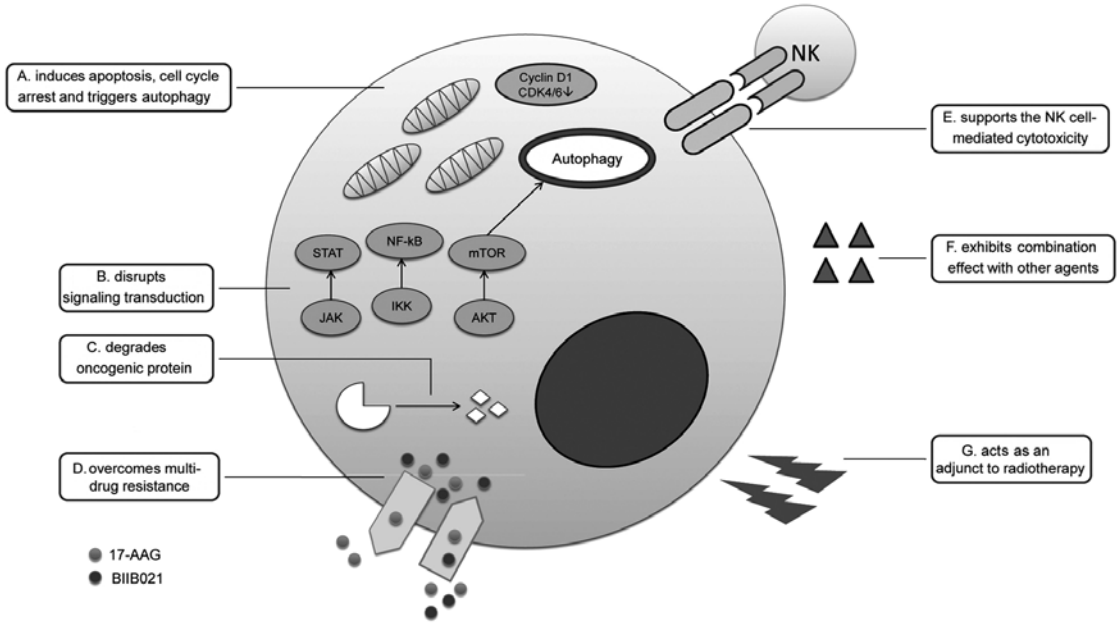

Figure 2. Mechanisms underlying the effects on cancer cells by BIIB021. BIIB021 induces apoptosis, cell cycle arrest and triggers autophagy of tumor cells (A). Treatment with BIIB021 disrupts signaling transduction (B), leads to degradation of oncogenic protein (C), overcomes multidrug resistance (D), supports NK cell-mediated cytotoxicity (E), acts as an adjunct to radiotherapy (G) and exhibits a combined effect with other agents (F).

Clinical trials. As the preclinical data suggest that Hsp90 inhibitors have anticancer activity via multiple mechanisms and are an attractive therapeutic strategy, clinical trials have been conducted to evaluate their MTD, safety and pharmacokinetic properties (Table I).

In a phase I study, 24 patients with advanced AML were enrolled and received escalating doses of 17-DMAG. This type of Hsp90 inhibitor was well tolerated with toxicities of neutropenic, fever, fatigue, nausea and diarrhea. The MTD recommended was 24 mg/m^2 on a twice-weekly dosing schedule. Two cases of cardiac DLT were observed at 32 mg/m^2. Compared with baseline, the apoptosis increased within leukemic marrow CD34$^+$ cells at day 15. Evidence of 17-DMAG antitumor activity included three patients which achieved a complete response (CR) with incomplete blood count recovery (CRi) and one had a >50% bone marrow blast reduction. Notably, among the 3 patients who had CRi, 2 showed del(7q) karyotype (119). Whereas, another phase I study indicated that 17-AAG had limited synergistic activity with Ara-C at clinically tolerable doses. Among 21 patients, 2 achieved CR and 4 had PR. The drug combination induced serious adverse effects: Disseminated intravascular coagulation (DIC), acute respiratory distress syndrome (ARDS) and myocardial infarction. A modest downregulation of Chk1 and other Hsp90 client proteins was observed. This may have resulted from Hsp70 upregulation caused by the two drugs and, at clinical tolerated dose, time was limited to sustain effective concentrations of 17-AAG that were able to downregulate substantial client proteins *in vivo* (120). Other Hsp90 inhibitors with reduced toxicity, better solubility and improved pharmacokinetics and pharmacodynamics should be developed and used in the treatment of AML.

The oncogenic process of multiple myeloma (MM) is not driven by classical client proteins of Hsp90. However, Hsp90 plays a critical role in the regulation of MM cell proliferation, survival, drug resistance and microenvironmental interactions. In a phase I/IB study, 24 patients with relapsed or refractory MM received NVP-AUY922 at doses ranging from 8 to 70 mg/m^2. At 70 mg/m^2, grade 3 blurred vision was observed while no MTD was reached. None of the patients achieved CR or PR. A total of 16/24 of the subjects had stable disease (SD). Another non-ansamycin, non-purine Hsp90 inhibitor, KW-2478, was administered intravenously in a phase I study in a dose range of 14 to 176 mg/m^2 and was well tolerated without DLTs. A total of 20 (95.2%) patients achieved SD among 24 evaluable patients (121). As *in vitro* and animal experiments suggest that 17-AAG synergizes with standard therapy bortezomib, a phase I/II clinical trial enrolled 72 patients with relapsed or refractory MM to assess the combined effect. On days 1, 4, 8 and 11 in each 21-day cycle, patients received 17-AAG (100-340 mg/m^2) and bortezomib (0.7-1.3 mg/m^2) in a phase I study while 17-AAG (340 mg/m^2) plus bortezomib (1.3 mg/m^2) was administered during the phase II expansion. Among the evaluable 67 patients, 2 patients (3%) had CR, 8 patients (12%) had PR, 8 patients (12%) had a minimal response and 22 patients (33%) experienced SD (122). Prior exposure and response to bortezomib dramatically influenced the response rates; the highest rates were in bortezomib-naive patients (10/21; 48%).

Hsp90 is commonly expressed in many types of B- and T-cell lymphoma and its client proteins are critical in cell proliferation and survival (40,67). Hence, many lymphoma types are suitable targets for Hsp90 inhibitors and clinical trials were also conducted to examine the effects of Hsp90 inhibitors on lymphoma. In a phase II study, 22 patients with relapsed lymphoma were enrolled and received 17-AAG at 220 mg/m^2. Seven of 18 patients suffered tumor reduction of whom 2 had PR (123). The biopsy specimens of MCL showed, after treatment of 17-AAG, the expression of p-AKT, cyclin D1 and Ki-67 declined while activation of caspase-3

increased. In addition, another open-label, single arm phase II study evaluated the efficacy of AUY922 against DLBCL and peripheral T-cell lymphoma (PTCL). After 2 cycles, 1/14 DLBCL patients achieved a CR and 1/6 PTCL patients achieved PR (124).

5. Conclusion

In an era of precision medicine, clinicians are able to design optimal therapies for patients with malignant tumors according to molecular analyses. Hsp90 inhibitors are a type of agents that target oncogenic proteins and signaling networks in several tumors by influencing protein post-translational maturation and disposition. Unfortunately, the clinical potency of first generation Hsp90 inhibitors is limited as natural product derivatives are toxic and have unfavorable pharmacokinetic properties.

BIIB021, as a fully synthetic small-molecule inhibitor, has shown effective antitumor potency. *In vitro* experiments have demonstrated that it induces apoptosis, cell cycle arrest and triggers autophagy of tumor cells. Treatment with BIIB021 led to degradation of oncogenic proteins, disrupted signaling transduction, supported NK cell-mediated cytotoxicity, acted as an adjunct to radiotherapy, overcame multi-drug resistance and exhibited combined effects with other agents (Fig. 2). Furthermore, this agent has advantages of good solubility and low toxicity. phase I/II trials indicate that the drug is active in serum, PBMCs and tumor tissue, is well tolerated and could lead to objective responses in refractory GIST patients (56,57). BIIB021 is a promising Hsp90 inhibitor that deserves further studies in regards to the treatment of patients with refractory or relapsed tumors especially in blood malignancies.

The efficacy of BIIB021 against leukemia and lymphoma allows us to focus on using this Hsp90 inhibitor in the treatment of blood malignancies. Indeed, the expression level of Hsp90 is high and is correlated with poor prognosis in leukemia and myeloma (64-67). Inhibition of Hsp90 can result in degradation of its client protein including Bcr-Abl, c-KIT and FLT3-ITD which are oncoproteins or constitutively activated in leukemia.

Pre-clinical data demonstrated that Hsp90 inhibitors lead to apoptosis of cancer cells by varied mechanisms. Clinical trials have demonstrated that Hsp90 inhibitors can enable a population of patients with relapsed or refractory blood malignancies to achieve CR, PR or SD (119,123,125) (Table I). However, single treatment with an Hsp90 inhibitor showed limited activity against various diseases (124). One potential solution may be combination therapy. Several *in vitro* studies have provided rationale for combining Hsp90 inhibitor with a number of other agents, including Ara-C, bortezomib, imatinib, histone deacetylase inhibitor and FLT3 inhibitor. In a phase I/II trial, 17-AAG + bortezomib were well tolerated and 27% patients with relapsed or refractory myeloma achieved objective response (122). In another phase I study, after exposure to 17-AAG + Ara-C, the overall response rate was 23% among 26 patients with relapsed and refractory acute leukemia (120). At tolerable doses, the time of 17-AAG for effective concentration was insufficient to decrease client proteins. This may contribute to the limited combination activity. It is expected that more clinical studies can be conducted to search for synergistic effects by using novel Hsp90 inhibitors with favorable pharmacologic properties.

In summary, BIIB021 is a novel agent in the fight against cancer and targeting Hsp90 is a promising therapeutic strategy for the management of blood malignancies.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

WH conceived and designed the study. WH and HXH researched the literature, performed analysis of data and drafted the manuscript. Both authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors state that they have no competing interests.

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